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1 **All non-adherence is equal, but is some more equal than others?**
2 **TB in the digital era.**

3
4 Helen R. Stagg¹; Mary Flook¹; Antal Martinecz^{2,3,4}; Karina Kielmann⁵; Pia Abel Zur
5 Wiesch^{2,3,*}; Aaron S Karat^{5,6,*}; Marc CI Lipman^{7,8,*}; Derek J Sloan^{9,*}; Elizabeth F. Walker¹⁰;
6 Katherine L Fielding^{11,12}

7
8 * Presented alphabetically; these four authors contributed equally to this work

9
10 ¹ Usher Institute, University of Edinburgh, Old Medical School, Teviot Place, Edinburgh, EH8
11 9AG, UK

12 ² Department of Biology, The Pennsylvania State University, University Park, PA 16802,
13 USA

14 ³ Center for Infectious Disease Dynamics, Huck Institutes of the Life Sciences, The
15 Pennsylvania State University, University Park, PA 16802, USA

16 ⁴ Department of Pharmacy, Faculty of Health Sciences, UiT- The Arctic University of Norway,
17 9037 Tromsø, Norway

18 ⁵ The Institute for Global Health and Development, Queen Margaret University, Queen
19 Margaret University Drive, Musselburgh, EH21 6UU, UK

20 ⁶ TB Centre, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E
21 7HT, UK

22 ⁷ UCL Respiratory, Division of Medicine, University College London, London, UK

23 ⁸ Department of Respiratory Medicine, Royal Free London NHS Foundation Trust, Pond
24 Street, London, NW3 2QG, UK, UK

25 ⁹ School of Medicine, University of St Andrews, St Andrews, KY16 9TF, UK

26 ¹⁰ London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

27 ¹¹ Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical
28 Medicine, Keppel Street, London, WC1E 7HT, UK

29 ¹² School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

30
31 Corresponding author: Dr. Helen R. Stagg; Usher Institute, University of Edinburgh, Old
32 Medical School, Teviot Place, Edinburgh, EH8 9AG, UK; helen.stagg@ed.ac.uk; +44131
33 651 1447

34
35 Take-home message: Digital adherence technologies (DATs) provide a wealth of information
36 on dose-by-dose anti-TB medication-taking. Studies of DAT data should place non-
37 adherence in standardised taxonomic frameworks in order to best inform intervention and
38 regimen design.
39

1 **Abstract**

2 Adherence to treatment for tuberculosis (TB) has been a concern for many decades,
3 resulting in the World Health Organization’s recommendation of the direct observation of
4 treatment in the 1990s. Recent advances in digital adherence technologies (DATs) have
5 renewed discussion on how to best address non-adherence, as well as offering important
6 information on dose-by-dose adherence patterns and their variability between countries and
7 settings. Previous studies have largely focussed on percentage thresholds to delineate
8 sufficient adherence, but this is misleading and limited, given the complex and dynamic
9 nature of adherence over the treatment course. Instead, we apply a standardised taxonomy-
10 as adopted by the international adherence community- to dose-by-dose medication-taking
11 data, which divides missed doses into a) late/non-initiation (starting treatment later than
12 expected/not starting), b) discontinuation (ending treatment early), and c) suboptimal
13 implementation (intermittent missed doses). Using this taxonomy, we can consider the
14 implications of different forms of non-adherence for intervention and regimen design. For
15 example, can treatment regimens be adapted to increase the ‘forgiveness’ of common
16 patterns of suboptimal implementation to protect against treatment failure and the
17 development of drug resistance? Is it reasonable to treat all missed doses of treatment as
18 equally problematic and equally common when deploying DATs? Can DAT data be used to
19 indicate the patients that need enhanced levels of support during their treatment course?
20 Critically, we pinpoint key areas where knowledge regarding treatment adherence is sparse
21 and impeding scientific progress.
22

1 Introduction

2 Many decades after initial trials of antimicrobials for TB,[1] the standard treatment for drug
3 sensitive disease remains lengthy at six months; regimens for drug resistant disease can last
4 for two years.[2] Concerns about adherence to treatment over such long periods - and the
5 implications of that non-adherence - led to the World Health Organization (WHO)
6 recommendation of directly observed treatment (DOT) in 1994.[3, 4]

7
8 In recent years, digital adherence technologies (DATs; including SMS-based reminders,
9 video supported therapy [VOT], and medication monitor boxes) have increasingly been
10 tested as remote alternatives to DOT/other standards of care as they may be cheaper, more
11 acceptable, and less financially and temporally burdensome.[5, 6] DATs provide healthcare
12 workers with regular, up-to-date, information on how medication has been taken (either
13 accessed at each appointment or remotely each day). DATs can be provided in different
14 ways, e.g. to all patients as the sole source of support or as part of a package of
15 interventions that is personalised to an individual's needs.[7] Intervention packages may be
16 reviewed as a result of appointment-by-appointment (or remote dose-by-dose) evaluation of
17 DAT data that demonstrates the need for enhanced treatment support.[8, 9] Such reviews
18 could also help to determine the patients least in need of dose-by-dose monitoring i.e.
19 providing a 'step-down' approach during treatment.

20
21 Like DOT, DATs are interventions to promote dose-taking that assumes all doses are of
22 equal importance. This one-size-fits-all approach latently assumes that missed doses are
23 essentially interchangeable i.e. that each is of equal importance in terms of its clinical
24 implications. This may not be the case; early stage adherence when bacterial loads are
25 higher may be more important than late stage, for example. Additionally, it is assumed that
26 DOT and DATs work equally well across the entire treatment period, which is not always the
27 case.[10]

28
29 The advent of DATs provides a unique moment to reassess our global approach to non-
30 adherence to anti-TB medications. Assuming that DAT event monitoring is equivalent to
31 dose-taking, DAT devices provide rich digital datasets of date- and time-stamped information
32 that have not previously been available to the research community. Key lessons about anti-
33 TB medication-taking and best practice for DAT deployment can be learnt, in order to avoid
34 a simple duplication of our current global DOT approach and better personalise clinical care.

35
36 In this paper, we take the opportunity of ongoing global evaluation and roll-out of DATs to
37 review and refine a classification of non-adherence to treatment, examine the evidence for
38 the global burden and association of different types of non-adherence with treatment
39 outcomes, and consider what this refined classification of non-adherence means for
40 intervention and regimen design and deployment.

41 What is non-adherence?

42
43 In this paper, we adopt a definition of adherence that emphasises the patient's role in
44 agreeing a treatment plan i.e.:

45 *Adherence- when a patient's dose-taking, at any stage during treatment, matches*
46 *mutually agreed recommendations from the prescriber.[11]*

47 Therefore, non-adherence represents a divergence from this agreement.

48
49 Traditionally, TB research has assessed non-adherence using simple 80-90% thresholds of
50 doses taken across the duration of treatment. To date, few studies have determined whether
51 80-90% is the optimal point of inflection. Furthermore, this simple binary classification masks
52 extensive complexity across the treatment period. Given this complexity, it is essential to lay
53 out definitions and descriptors.[12, 13] In 2010, partly co-ordinated by the European Society
54 for Patient Adherence, Compliance and Persistence (ESPACOMP), a new taxonomy for

1 non-adherence was launched.[14] This is the only globally accepted taxonomy for non-
2 adherence, which consists of three core concepts, which are mappable using dose-by-dose
3 data, such as that provided by DATs (Figure 1a) and b)):

- 4 1) Initiation, which tracks when the first dose of a regimen is taken relative to the
5 intended start date.
- 6 2) Discontinuation, which documents the cessation of treatment.
- 7 3) Implementation- how doses are taken during the period of persistence (the
8 timeframe between initiation and discontinuation) i.e. intermittent missed doses
9 (treatment gaps).

10
11 As a condition with a time-limited treatment period, TB lends itself to this definitions
12 framework. Drug-sensitive TB is treated for six months with an all-oral regimen, starting with
13 four drugs administered over two months (initiation phase; not to be confused with treatment
14 initiation), followed by two drugs over four months (continuation phase).[15] It is usually
15 dosed daily; in some places, thrice-weekly regimens (although problematic in their own right,
16 see below) are utilised to allow to make DOT less burdensome on both the patient and the
17 healthcare system. Fixed dose combination (FDC) pills are used in many settings. Thus the
18 number of treatment doses expected to be taken in a week can vary from place to place and
19 patient to patient; the number of pills this represents will also vary depending upon a
20 patient's weight. For drug-resistant TB, both regimens themselves and their dosing becomes
21 more complex, and treatment more lengthy.[16]

22
23 Within the context of non-adherence to TB treatment, the core concepts can be mapped as
24 follows:

- 25 1) Late initiation of, or not initiating, treatment: this charts the time frame between the
26 intended treatment start date after a patient is informed of their diagnosis and the
27 first dose being taken. The reasons for issues with initiation are multifactorial.
28 Delays can be due to a lag in, or non-acquisition of, medication, as well as
29 provided medication not being taken. Non-initiation may be driven by failures in
30 the access of/linkage to care cascade with drivers and consequences that are,
31 therefore, different from late initiation.
- 32 2) Early discontinuation of treatment e.g. due to loss to follow-up (LFU; previously
33 known as default).[17]
- 34 3) Suboptimal implementation,[12] i.e. the form of non-adherence that has been the
35 focus of both observational studies and clinical trials.

36
37
38 Of note, LFU - as defined by the WHO[17] - is not a clear-cut proxy for early discontinuation
39 of treatment. This is because it is both a standardised end-of-treatment outcome that is
40 reported within surveillance systems (treatment is interrupted for two consecutive months or
41 more), as well as occurring when a TB patient does not start treatment ('initial LFU' or 'pre-
42 treatment LFU').[18, 19] LFU thus a) contains some non-initiation and b) is not the only form
43 of discontinuation due to the time constriction placed upon it. Furthermore, LFU documents
44 non-engagement with clinical appointments, not medication-taking *per se*.

45
46 In the next sections, we will discuss how the effect of the three core concepts of non-
47 adherence on TB control depends on two factors: 1) the prevalence of each kind of non-
48 adherence and 2) the impact of each type on treatment outcomes. Throughout this paper,
49 we use a previously published dataset of DAT data to provide a worked example of the
50 concepts that we illustrate (Table 1).

1 **Late or non-initiation**

2 ***What is the global burden?***

3 Among our core components of non-adherence, non-initiation is arguably most on the global
4 map, as a component part of the WHO's campaign to find and treat the 'missing millions'. [20]
5 The precise number of patients not starting treatment is unknown, although WHO estimates
6 treatment coverage to be 69% globally. [21] For rifampicin-resistant TB, Boyd *et al.* have
7 estimated a similar global mean of 76% of individuals initiating treatment, among those
8 diagnosed. [22] In a review of studies undertaken in low-income and lower-middle-income
9 countries, or those with a high burden of TB, MacPherson *et al.* projected that 18% of
10 individuals do not initiate treatment after diagnosis in African nations and 13% in Asian
11 nations. [18] A later study estimated the figure to be 12% in South Africa. [19]

12
13 A series of systematic reviews and meta-analyses have examined temporal delays in
14 treatment initiation (the time frame between diagnosis and the start of treatment). In India
15 among pulmonary TB patients, median delay was 2.5 days (IQR 1.9-3.6) [23] and in the
16 Eastern Mediterranean Region zero to two days. [24] In comparison, a recent observational
17 study from China found the median time from TB diagnosis to MDR TB treatment was six
18 months. [25] This is because the situation in drug resistant disease is additionally complex,
19 as patients may start on the six month regimen whilst waiting for drug sensitivity testing
20 results before their treatment is adjusted (proving a window for further drug resistance to
21 develop), [16] and sourcing second-line drugs may take time.

22 23 ***What is the relationship with treatment outcomes?***

24 Examining the relationship between initiation of treatment and treatment outcomes is
25 complicated by the different measures of lateness used in the literature. In many papers, an
26 overall figure of the delay between symptoms and the start of treatment was quoted, rather
27 than delays between diagnosis and the start of treatment (Figure 2). *In sensu stricto*, we
28 sought to document delays between diagnosis (preferably when it was received by the
29 patient) and the start of treatment only.

30
31 In a 2018 review, Melsew *et al.* examined the impact of delays in starting treatment on
32 patient infectiousness. [26] Among eight studies, four found evidence for an association
33 between delays in treatment initiation after the onset of symptoms (with a roughly doubling of
34 the odds of infectiousness), three found no evidence for an association, and one found
35 mixed evidence. The delays charted were from less than a fortnight to more than 90 days.

36
37 Evidence from Ethiopia documented a doubling in the adjusted relative risk of treatment
38 failure, death or LFU among those for whom delay was >30 days. [27] This study used a
39 measure of 'overall delay' (from the start of symptoms to the start of treatment) with a
40 median of 55 days (inter-quartile range [IQR] 32-100) documented. Of this, 22 days (9-48)
41 were classed as 'provider delay' i.e. the time post-presentation at a healthcare facility
42 between diagnosis and the start of treatment.

43
44 Among MDR patients in Myanmar, in a univariable analysis where treatment delay was
45 classified as between the date of MDR-TB confirmation and the date of treatment initiation,
46 the median treatment delay for patients with poor treatment outcomes (lost to follow up,
47 failed, died) was 144 days, which was longer than among patients who achieved successful
48 treatment outcomes (102 days). [28] In an adjusted analysis comparing the impact of long
49 (\geq median of 152 days) versus short ($<$ median) delays, this association was not retained.

50
51 In MDR TB patients in China results were also mixed, this time depending upon the measure
52 of delay used. The time between TB diagnosis to the start of MDR treatment showed some
53 effect, albeit with a null-inclusive confidence interval, whereas shorter delays (\leq 60 days)
54 after the performance of DST showed a doubling or more in the likelihood of a positive
55 treatment outcome, depending upon the other factors adjusted for. [25]

1 **Discontinuation**

2 ***What is the global burden?***

3 Due to the substantial overlap with LFU and the use of this measure as a standardised
4 reporting outcome, the estimates of the global burden of discontinuation have been captured
5 in many studies. An individual patient data meta-analysis of 9,000 MDR TB patients from 23
6 countries suggested around a sixth were lost to follow up, with a median timing of seven
7 months.[29] In an older systematic review not specifically for drug-resistant disease, Kruk *et*
8 *al.* documented likelihoods of LFU of 7-54% and timings of between 42 and 85 days in low-
9 and middle-income settings.[30] There was large amounts of variation between countries
10 and regions. Approaches that include a precise analysis of when discontinuation from
11 treatment occurs and how this relates to LFU should become more common as dose-by-
12 dose monitoring systems are rolled out globally.

14 ***What is the relationship with treatment outcomes?***

15 Determining the relationship between discontinuation and treatment outcomes is complex,
16 given the use of LFU both as a marker of discontinuation and a negative surveillance
17 outcome.[17] Useful sources of data include the randomised controlled trials (RCTs) that
18 developed the standard regimen we use today. Historically, it was the addition of rifampicin
19 and then pyrazinamide which allowed treatment to be shortened to six months;[31] further
20 studies showed an important increase in the likelihood of post-treatment relapse when
21 treatment was reduced to four months.[32]

23 In recent years, several RCTs have sought to shorten the treatment of drug sensitive TB to
24 four months by including fluoroquinolones, but, as yet, none have demonstrated non-
25 inferiority.[33-35] Pooled analyses have indicated that such regimens may be non-inferior in
26 particular patient groups, indicating the need for stratified treatment approaches.[36]
27 Although such regimens are intended to reduce non-adherence by shortening overall
28 duration, this may increase the sensitivity of such regimens to suboptimal implementation i.e.
29 the importance of each dose in the regimen may be increased, relative to a longer regimen,
30 making each missed dose more problematic.

32 Critically, well-designed studies using dose-by-dose monitoring systems such as DATs
33 together with robust treatment outcome collection will go a long way towards answering
34 remaining questions in this area.

36 **Suboptimal implementation**

37 ***What is the global burden?***

38 Until recently, suboptimal implementation for anti-TB treatment has been assessed through
39 the differentially reliable self-reported or questionnaire-derived methods (for example [37,
40 38]) and DOT (e.g. [10, 39-41]). Study protocols also used various thresholds to classify
41 non-adherence, and often reported a mixture of suboptimal implementation and
42 discontinuation in their analyses.

44 To date, the burden of suboptimal implementation is suggested to be highly variable
45 between countries and regions, e.g. 21·3% in pooled estimate from Ethiopia versus 90·8% in
46 the Philippines, although differences will partly be protocol-dependent.[41, 42] Approaches
47 that include a precise analysis of the types of suboptimal implementation displayed by
48 patients should become more common as dose-by-dose monitoring systems are rolled out
49 globally,[43] e.g. examining the lengths of gaps displayed and when they occur during
50 treatment.[12, 44] For example, in a recent study in China, 47·2% of 780 patients had a
51 dosing gap of a week or more and 95·9% some form of suboptimal implementation (Table
52 1).[12]

1 **What is the relationship with treatment outcomes?**

2 There has been substantial interest in the relationship between suboptimal implementation
3 and various intermediate and final treatment outcomes. Largely using simple percentage
4 adherence thresholds across the entire treatment period, suboptimal implementation has
5 been associated with unsuccessful treatment outcomes in a variety of settings from Malawi
6 to Israel, in both observational and randomised controlled trial datasets, and using a variety
7 of methods to define and measure implementation.[36, 44-49] In observational datasets from
8 Russia and the US, this association extends to the development of drug resistance,[50, 51]
9 although in simulations it has not been consistently proven.[52] Recurrence of TB disease
10 among pulmonary TB patients was higher with worse implementation in both the Yemen and
11 Vietnam.[53, 54]

12
13 Moving beyond adherence thresholds, in MDR TB patients in Armenia and Abkhazia on
14 DOT, Bastard *et al.* noted the criticality of gap length and the time between gaps. Odds of
15 negative outcomes (treatment failure, death or default) nearly quadrupled with interruptions
16 of three or more days and also short periods (<10 days) between gaps.[44] From a different
17 angle in drug-sensitive pulmonary TB, Johnston *et al.*'s meta-regression found that treatment
18 failure, acquired drug resistance, and relapse were more common with thrice-weekly versus
19 daily dosing.[55] The Imperial *et al.* pooled meta-analysis looked at the impact of a six days
20 in seven versus a seven days in seven dosing strategy and found that the former increased
21 the likelihood of an unfavourable outcome (broadly death, treatment failure, a lack of culture
22 conversion, relapse, adverse events), as well as the implications of different adherence
23 thresholds within this.[36]

24
25 As for discontinuation, well-designed studies using DATs or other dose-by-dose monitoring
26 systems will be essential to answer the remaining questions in this area.

27
28 **What do different types of non-adherence mean for intervention and regimen
29 design and deployment?**

30 Effectively preventing non-adherence to treatment not only requires interventions
31 appropriately tailored to patients and healthcare systems, but also the type of non-
32 adherence commonly displayed. Critically, the types of non-adherence displayed and their
33 relationship to treatment outcomes may vary by population group e.g. people living with HIV,
34 individuals with other comorbidities, children and the elderly. Elucidating these relationships
35 requires setting-by-setting data collection using tools such as DATs. This should include how
36 variability in adherence throughout treatment determines the need for 'step-up' interventions.

37
38 **Late or non-initiation**

39 Non-initiation of treatment after diagnosis can be due to a large number of complex factors,
40 including the lack of accessibility of treatment - e.g. due to costs associated with attending
41 the clinic; under-resourced or poorly functioning facilities; and stigma/lack of awareness of
42 TB.[56-58] Here, interventions include broad systems-strengthening factors that will benefit
43 the entire care cascade, such as better financing of healthcare systems; the provision of free
44 TB drugs to everyone; and the removal of other financial barriers e.g. through cash transfer
45 programmes,[59] as well as 'pull factors' such as improvement of the quality of care;
46 increasing awareness of/decreasing stigma around TB; and improving case
47 detection/outreach. Factors such as strengthening the care cascade and reducing stigma
48 may reduce late initiation, too.

49
50 **Discontinuation**

51 If discontinuation occurs early enough, even if it is relatively uncommon, it can form a large
52 proportion of missed doses during treatment (Figure 1c). As documented above, early
53 discontinuation is also known to be highly detrimental to treatment outcomes. Therefore,
54 settings should consider the relative burden of discontinuation versus other forms of non-

1 adherence when planning for effective interventions to implement (Table 1).

2
3 When it comes to intervention design, a single intervention may not address all
4 discontinuation, as the drivers are not the same for every patient and sometimes reflect
5 disengagement with care, rather than treatment.

6
7 One of the key implications for the development of shorter treatment regimens is their
8 potential to reduce discontinuation,[60] simply by reducing overall duration (Table 1).

9 ***Suboptimal implementation and interventions***

10 Intelligent intervention design should be influenced by the common form of suboptimal
11 implementation (including long versus short gaps and erratic versus regular missed doses;
12 Figure 1d), their causes (i.e. treatment-related, individual knowledge and perceptions, social
13 factors, systems issues, temporal factors, and structural factors.[61-64] Also influential, is
14 whether non-adherence is intentional or unintentional,[11] however; making the distinction
15 on an individual basis can be difficult and potentially fruitless.

16
17
18 To date, many interventions have sought to target individual-level cognitive or behavioural
19 factors such as forgetfulness or 'misconceptions' through SMS reminder systems,
20 medication monitor box alarms, or the regular need to report for DOT or VOT.[43] More
21 complex interventions are required to deal with multifactorial causes of non-adherence,[7]
22 such as rapid reporting and support systems. As TB tends to affect socially and
23 economically deprived groups, interventions that focus on individual agency and behaviour-
24 but do not account for social and structural barriers to care (as well as factors that influence
25 a patient's ability to take medication regularly) - are destined to work primarily for those who
26 already have better capacity and social circumstances.[65]

27
28 Critically, adherence to treatment is dynamic and can change in response to events and life
29 circumstances of all kinds over time,[66] producing ever-varying patterns of suboptimal
30 implementation. Dose-by-dose monitoring systems that are accessible to healthcare
31 services can be used to promote rapid responsiveness to the frequency and length of gaps
32 that occur during treatment (Table 1), as part of the partnership between patients and
33 healthcare providers.[67]

34
35 Polypharmacy is of substantial concern as a cause of non-adherence,[68] and therefore
36 population groups for whom this is an issue should have special consideration in intervention
37 design.

38 ***Suboptimal implementation and regimen forgiveness***

39 The 'forgiveness' of treatment regimens reflects their ability to withstand unexpected gaps in
40 dosing.[69] Forgiveness varies from drug to drug, depending on pharmacokinetic
41 parameters, thus each drug will respond individually to different patterns of suboptimal
42 implementation. The development of drug resistance is a key consideration; differing gap
43 lengths can lead to divergent results. Within multidrug regimens, such as those used for TB,
44 the maintenance of sufficient drug blood levels to achieve an antibacterial effect depends
45 upon the metabolism of all the component drugs and thus how they behave in combination.
46 Dosing strategies may potentially be alterable to overcome non-forgiveness, but this should
47 be undertaken in light of considerations surrounding the patient's medication-taking burden
48 (e.g. the number of times doses need to be taken in a day) and whether or not combined
49 pills containing different drugs of different characteristics are used.[70, 71]

50
51
52 We provide two illustrations: not taking any treatment at a given time point versus not taking
53 some of the drugs.

54
55 When all drugs are omitted at the same time, the implications of longer and shorter breaks

1 should be considered separately. Longer gaps from treatment (four days or more) can allow
2 bacteria to restart replication. It is currently unknown how such an increase in the bacterial
3 burden may affect treatment outcomes; it may prolong the treatment length required for a
4 cure. Here, replication after previous exposure to antibiotics may facilitate the emergence of
5 resistance.

6
7 Shorter breaks (one to two days; Table 1) may be a problem when different drugs within a
8 combination regimen have different pharmacokinetic properties and therefore some may
9 take a considerably longer time to clear and/or reach their therapeutic levels when the
10 regimen is re-started. As a result, drug concentrations after the first dose and at steady state
11 will differ considerably in some tissues or plasma. For example, Strydom *et al.* have
12 illustrated the effects of the slower accumulation of certain drugs in a pharmacokinetics
13 study on TB patients undergoing lung resection surgery.[72] In the most detailed study of its
14 kind, the authors demonstrated that drug concentrations after the first dose of a drug differ
15 from those at steady state - at least in some tissues - for ethambutol (shown in a different
16 study[73]), pyrazinamide, moxifloxacin, and linezolid. This was not the case for isoniazid,
17 rifampicin, and kanamycin. More studies of this type will help us understand how TB drugs
18 accumulate and behave in relevant lesion types.

19
20 During instances when all drugs are omitted at the same time, the drug that clears more
21 slowly will be still present after others, resulting in effective monotherapy during the gap.
22 Even with perfect adherence, it is known that there are periods of effective monotherapy
23 within each day.[72] The impact of such short bouts of monotherapy on the emergence of
24 resistance is largely unknown. Drugs that require multiple days to reach their steady state
25 levels may be below their therapeutic ranges for days after treatment resumes. Frequent
26 short gaps may therefore keep levels below the therapeutic range for a longer period.
27 Illustrations of how this would impact rifampicin and moxifloxacin levels in the lungs are
28 presented (Figure 3).

29
30 If FDCs are not used, it is also possible to suboptimally implement specific components of
31 the regimen. During the continuation phase of treatment, suboptimal implementation of one
32 drug will lead to monotherapy; the risk of drug resistance posed by monotherapy was
33 illustrated by one of the first rifampicin trials in 1968.[74, 75] As a result, the current ethical
34 maximum for monotherapy studies is 14 days.[76]

35
36 Further data in this area are required to better understand how gap lengths, timings and
37 frequencies of suboptimal implementation carry the most risk for the emergence of
38 resistance or in prolonging treatments, and how this is influenced by patient-by-patient
39 variability in pharmacokinetics (e.g. isoniazid acetylase status) and clinical characteristics
40 known to influence treatment success.[36]

41 42 ***The relationship between different types of non-adherence***

43 In addition to considering the different types of non-adherence in isolation, the relationships
44 between them also have important implications for intervention design. For example, an
45 approximate doubling in the likelihood of discontinuation in the presence of suboptimal
46 implementation of <80% versus ≥90% during the initiation phase of treatment has been
47 demonstrated in data from China (Table 1).[9, 12] Early-stage dose-by-dose monitoring data
48 from DATs could thus be highly valuable at indicating the patients who will later be in need of
49 additional adherence support.

50 51 **Latent tuberculosis**

52 In our consideration of adherence to TB treatment up to this point, our focus has been on TB
53 disease. Needless to say, the issues raised are equally important for latent tuberculosis
54 infection (LTBI) and preventive treatment; there is still a need for a standardised taxonomic
55 framework within which to discuss non-adherence. Unlike for drug sensitive TB disease,

1 adherence studies for LTBI need to take into account the different WHO-recommended
2 regimen lengths and dosing patterns when applying this framework.[77]

3
4 Numerous studies have documented how adherent patients are to LTBI treatment; such
5 studies have a far greater focus on non-initiation than studies of treatment for TB disease,
6 given the interest in a) patients declining take preferred treatment or b) not being offered
7 treatment.[78, 79] Additionally, the nature of LTBI makes treatment completion the marker of
8 choice for treatment success by National TB Programmes, thus the proportion of patients
9 completing treatment has been extensively reviewed.[78-81] For both non-initiation and
10 discontinuation, levels were highly variable between studies (7-99% and 4-100%,
11 respectively). A global consensus as to which non-adherence patterns can be safely
12 tolerated for LTBI regimens of different lengths is urgently needed. As with TB disease, this
13 should also influence the design of interventions to promote adherence, as well as decisions
14 on which regimens will be most effective in a given population group (balancing cost; the
15 length of the regimen, its adverse event profile and the implications for adherence; and
16 regimen efficacy).

17 18 19 **Conclusion**

20 As a global TB community, we find ourselves at a crossroads when it comes to treatment
21 adherence. Through DATs, remote dose-by-dose treatment monitoring has become
22 accessible like never before, and we have a substantial opportunity to deploy precision
23 medicine approaches to develop and target adherence-promoting interventions. In the
24 COVID-19 era, remote monitoring tools are all the more important for TB control due to the
25 need to reduce patient contact with healthcare services (and we also note the likely impact
26 of the disruption of the pandemic on adherence itself).

27
28 Important information is, however, missing. Further studies using tools such as DATs need
29 to be rapidly undertaken to fill critical gaps in our knowledge where only limited data exist
30 (Table 2). It is essential that interventions are not adopted at the national scale without
31 rigorous effectiveness and cost-effectiveness studies, such as that being undertaken by the
32 ASCENT project across five countries.[82] During adoption, careful programmatic
33 management is also required to avoid the wasteful parallel development of digital tools to
34 report and manage DAT data.[83]

35
36 Although we advocate in this paper for non-adherence to be considered as three separate
37 issues, it is important to note that the underlying causes of each component may be similar
38 and that each component may be inter-related. Effective interventions (such as those taking
39 a stepped approach to enhanced treatment support e.g. by more frequent contact with
40 health systems or resolution of insecure housing, etc.), may work across several
41 components of non-adherence, but this will not be known unless data are analysed in this
42 fashion. Trials of different interventions should also seek to separate their impact on the
43 different components of non-adherence.[13]

44
45 The data that arise from studies such as those we propose will raise crucial questions for the
46 future of TB control. For example, are levels of particularly problematic adherence issues low
47 enough globally that it is not necessary to watch patients taking every single dose of their
48 medication? Or should all patients be observed during the initiation phase, given the
49 medication burden, higher replicating mycobacterial load, and connection between early
50 suboptimal adherence and discontinuation, then allowed to self-medicate if no issues are
51 observed? Can culturally-adapted menus of interventions be developed to address the
52 common forms of non-adherence for any given setting? Can we build predictive models to
53 determine which patients are most likely to suffer from which problematic non-adherence
54 issues?

1 To date, the TB literature has largely treated all missed doses of treatment as equally
2 problematic and equally common. By harnessing the power of dose-by-dose adherence
3 data, particularly through DATs, we can determine which patterns of missingness are 'more
4 equal than others' - a finding that could revolutionise our approach to non-adherence.
5
6

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17

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27 for the decision to submit for publication.
28

29 **Authors contributions**

30 All authors contributed to the conception of the work. MF, HRS, AM and PAzW contributed
31 to the acquisition, analysis and interpretation of data/literature for the work. All authors
32 drafted the work/revised it critically for important intellectual content. All authors give final
33 approval of the manuscript version to be published and agree to be accountable for all
34 aspects of the work in ensuring that questions related to the accuracy or integrity of any part
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36

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1 **Tables**

2 **Table 1. The implications of non-adherence patterns for intervention and regimen**
 3 **design: worked example from China**

4 In a study of 780 patients from a pragmatic cluster-randomized trial in China of electronic reminders to
 5 improve treatment adherence,[9, 12] data were taken from the control arm of the trial (electronic
 6 reminders set to silent, thus no intervention to promote adherence). Medication monitor boxes
 7 provided granular data as to whether each individual dose was taken (box opening used as a proxy).
 8 Treatment was dosed every other day. All patients initiated treatment within this study. Decision
 9 making as which type of non-adherence should be targeted by interventions will also depend upon the
 10 relative impact of each form of non-adherence on outcomes.[84]

Domain	Suboptimal implementation	Discontinuation
Number of participants affected	748/780 (95.9%) of all participants suboptimally implemented their treatment.	235/780 (30.1%) of all participants discontinued early.
Number of doses missed	9,487/16,794 (56.4%) missed doses were due to suboptimal implementation.	7,307/16,794 (43.5%) missed doses were due to early discontinuation.
Patterns displayed	The median gap length per patient was one dose, with a maximum number of gaps per participant of 24. 176/780 individuals (22.6%) had gaps of seven doses (a fortnight) or more. Suboptimal implementation increased over time.	5.1% of individuals had discontinued treatment by the end of month two, 14.4% by the end of month four, 18.2% by the end of month five, 36.3% by the end of month six (including individuals missing only their last dose).
Link between suboptimal implementation and discontinuation?	Missed doses in the initiation phase due to suboptimal implementation associated with increased risk of discontinuation in the continuation phase.	
Implications for intervention and regimen design	The causes of large numbers of short gaps need to be ascertained and addressed by an effective intervention.	Given the burden of discontinuation and when it occurs, shortened regimens may have been helpful in this setting. Early stage suboptimal implementation could act as an indicator of patients who require an intervention to prevent discontinuation.

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1 **Table 2. Summary of knowledge gaps**

Area	Missing information	Impact
Global burden of different types of non-adherence	A better determination of the distribution of non-adherence between late/non-initiation, suboptimal implementation and discontinuation Whether there are substantial differences between (and within) countries. Who displays each pattern Why different patterns are displayed	Stratification of settings/populations on the basis of the interventions that might be useful, including changes to healthcare processes and systems Intelligent intervention design
Trials vs. normal treatment pathway	The extent to which non-adherence varies between clinical trials and in normal care settings	Aids decision-making surrounding the adoption of new regimens (operational efficacy)
Suboptimal implementation patterns	Improved estimates of the frequency and types of suboptimal implementation, explicitly excluding doses missed due to discontinuation Variability in patterns between settings and patients Causes of these patterns	Stratification of settings (e.g. by healthcare system)/populations (e.g. by patient characteristics) on the basis of the interventions that might be useful Intelligent intervention design
Relationship between the different components of adherence	Whether early-stage indicators of non-adherence can predict later issues with non-adherence	Inform clinicians as to which non-adherence patterns should trigger active intervention
Relationship between patterns and patient outcomes	Specific mapping of how different non-adherence types and patterns impact treatment failure (and the need to restart treatment) and the development of drug resistance, in order to prioritise cost-effective intervention development and roll-out	Stratification of settings/populations on the basis of the interventions that might be useful and when they should be 'stepped up' Intelligent intervention design Inform clinicians as to which non-adherence patterns should trigger active intervention
Regimen forgiveness	The impact of the commonly displayed adherence patterns on forgiveness The implications of non-adherence to each drug within the multidrug regimen	Inform regimen design

2

1 **Figure legends**

2 **Figure 1. The different components of non-adherence to treatment**

3 Using the standard taxonomy described by Vrijens *et al.*,[14] it is possible to distinguish between the
4 first and last prescribed doses of medication and the first and last doses taken. In terms of sources of
5 non-adherence- panel a)- firstly individuals may initiate treatment later than agreed with their clinician.
6 Secondly, treatment may be discontinued early i.e. before the last prescribed dose. Persistence is the
7 period between initiation and discontinuation. Thirdly- panel b)- non-adherence arises from how
8 individuals implement their medication; doses may be missed intermittently. In this diagram, the
9 complete regimen is only 10 doses. Adapted from Vrijens *et al.*[14] Panel c) illustrates the impact of
10 discontinuation within an illustrated population of eight patients taking six doses of treatment each
11 before treatment is stopped. 38% (1 - 3) discontinue their treatment early, all at different time points.
12 75% of patients (3-8) display some form of suboptimal implementation. Despite this, doses missed
13 due to discontinuation make up half of non-adherence across the entire patient population. Panel d)
14 illustrates different types of suboptimal implementation. Patient 1- short, irregular, gaps. Patient 2-
15 long, irregular, gaps. Patient 3- regular gaps. Treatment is not stopped after the last illustrated dose.
16 Green- dose taken, white- missed due to suboptimal implementation, orange- missed due to
17 discontinuation.
18

19 **Figure 2. Cascade of care until the start of tuberculosis treatment**

20 *These two time points may be on the same day. †For drug resistant tuberculosis patients, drug
21 sensitivity testing results may not be available until after treatment for drug sensitive disease is
22 initiated, necessitating a chance in regimen.
23

24 **Figure 3. Different patterns in suboptimal implementation lead to divergent results.**

25 Rifampicin (red, 600mg dose) and moxifloxacin (black, 400mg dose) concentrations were modelled in
26 uninvolved lung tissues. This combination is currently being investigated in clinical trials,[85] but the
27 two drugs have very different pharmacokinetic properties. The three different plots show the same
28 suboptimal implementation patterns as Figure 1d). Patient 1- short, irregular gaps. Patient 2- long,
29 irregular gaps. Patient 3- regular gaps. The different shaded areas indicate different issues with drug
30 concentrations. Cream indicates periods where only moxifloxacin is above the minimum inhibitory
31 concentration (MIC). Above the MIC the drug either stops replication completely or eliminates
32 bacteria, therefore during these periods there is an effective moxifloxacin monotherapy. Grey areas
33 are periods where no drug is above the MIC; as a result, bacteria may eventually restart replication.
34 Dark blue periods are when moxifloxacin concentrations do not reach the levels (therapeutic range)
35 expected during proper adherence. In these cases, bacterial elimination rates for the given period
36 may be lower than expected, therefore possibly delaying the time it takes to clear bacteria. The
37 presented MIC cut-offs are mainly for illustration purposes, to indicate time periods where adverse
38 events may occur due to differences in concentrations, rather than capturing events on a bacterial
39 population level. Bacterial population dynamics are governed by multiple factors in addition to drug
40 concentrations e.g. the post-antibiotic effect. For instance, growth rates of bacteria may be affected by
41 the post-antibiotic effect.[86] Furthermore, selection of resistance mechanisms also occurs at sub-
42 MIC concentrations.[87] The plots were made with the model and parameters published by Strydom
43 *et al.*[72]